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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,472	04/25/2000	Michael R. Bristow	MYOG:004DIV1	8819

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EXAMINER
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ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 11/27/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/558,472	BRISTOW ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 9/17/01 in Paper No. 6, has been entered.

Claim 23 has been amended.

Claims 17-22 have been cancelled.

Claim 23 is currently pending under examination.

Any rejection made of record in the prior Office action mailed 3/01/00 (Paper No. 4) and not made of record in the instant Office action has been withdrawn in view of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claim 23 under 35 U.S.C. 112, first paragraph, is maintained for reasons of record advanced on pages 5-9 of the prior Office action, mailed 5/11/01 (Paper No. 5).

Applicants argue that the Examiner is incorrect in arguing that there is insufficient evidence of increased α-MHC expression leading to patient benefit (see p. 4, 1st paragraph). Applicants provide an accompanying Gorczynski declaration as proof. It is noted that the Examiner stated that an increase in the amount of α-MHC mRNA in myocardial tissue would not provide a prediction of gene therapy for a subject having myocardial therapy. That is to say, there is no prediction based on the Declarant's statements that sufficient expression can be obtained by administration of a DNA

sequence encoding α-MHC. The Examiner does not dispute that there is an observed up-regulation of endogenous α-MHC mRNA in myocardial tissue in human subjects suffering from cardiomyopathy, after receiving medical treatment with β-andrenergic blocking agents as described in Example 5 of the instant specification. Indeed, the Gorczynski declaration provided with Applicants' response states that, "The study takes advantage of the fact that β-andrenergic blocking, such as metoprolo and carvedilol, effectively improve systolic function and reverse the dilated cardiomyopathy phenotype. Thus, monitoring gene expression levels as a correlate of improvement in the phenotype provides valuable evidence regarding a relationship between expression of various genes and the disease state itself." (See p. 3, 2nd paragraph of the Gorczynski declaration). However, these statements do not provide a correlation with the present specification, that any route of delivery, any promoter and any vector/delivery system provide sufficient production of α-MHC to affect myocardial failure. Applicants argue that the results provided by the instant specification and the Gorczynski declaration provide evidence for the correlation between levels of α and β-MHC and myocardial failure (see p. 4, 1st paragraph of the response).

The argument presented by the Examiner is directed to gene therapy employing an exogenous α-MHC transgene or DNA sequence, not the monitoring of the expression levels of endogenous α-MHC with correlation to a disease-state phenotype. The claimed invention is directed to a method of treating myocardial failure in a human comprising administration of an effective amount of a transgene encoding for α-MHC. As indicated in the prior Office action, the specification fails to teach the level of α-MHC transgene expression in myocardial tissue necessary to achieve treatment of

myocardial failure in a human subject. Furthermore, the specification fails to address how to overcome the unpredictable parameters in the gene therapy art (see Eck & Wilson, Deonarian, Verma and Crystal, pp. 5-7 of the prior Office action) and in particular, cardiovascular gene therapy (see Nabel and Hajjar pp. 8-9 of the prior Office action). The rejection or question in view of the guidance in the specification, along with that in the art, is whether sufficient expression can be achieved by the exogenously administrated α-MHC DNA sequence to have any effect of myocardial failure in a human.

Applicants argue that the Examiner disputes that there is insufficient evidence that therapeutic benefit can be achieved *in vivo* by the claimed method and provide evidence that following treatment of β-adrenergic blocking agents, patients with the idiopathic dilated cardiomyopathy phenotype exhibited mRNA levels of α-MHC increased, and mRNA levels of β-MHC levels decreased (see p. 4, 2nd paragraph of Applicants' Response). Applicants argue that this showing refutes the Examiner's position regarding *in vivo* efficacy. Applicants further argue that by monitoring gene expression levels in an intact heart as the ***phenotype is modified*** leads to a more direct assessment of potential correlating factors. Applicants argue that by measuring gene expression levels from an intact heart, one can view data in the presence of the net regulatory influences. Applicants argue that the exemplified study show a clear correlation between endogenous α- and β-MHC levels *in vivo* and the diseased state of the heart (see p. 5, 1st paragraph of Applicants' response). Applicants state that the Examiner's argument that the amount of expression needed to achieve clinical benefit is not understood (see p. 5, 2nd paragraph). To clarify, it is noted that the Examiner is not

disputing a role of α-MHC in myocardial failure, the Examiner's argument is directed to the unpredictable state of the art of gene therapy, and the lack of teaching or guidance provided by the instant specification in view of the art at the time of filing, to offer a protocol for achieving therapeutic levels of expression of an α-MHC transgene *in vivo* thereby providing therapy for a patient suffering from myocardial failure. Furthermore, the specification fails to provide guidance or teachings for the levels of α-MHC transgene expression would provide the therapeutic effect.

Again, as stated previously, the Examiner's argument is directed to the unpredictable state of the gene therapy art, both in a general sense, and with particular regard to cardiovascular gene therapy, and furthermore, with particular regard to the expression of an α-MHC transgene; the Examiner's argument is not directed to the correlation of endogenous α-MHC expression with correlation to a disease-state phenotype. Furthermore, although Applicant provides an example of monitoring endogenous α-MHC mRNA levels *in vivo* to provide evidence to improved cardiac output, Applicant has not provided guidance or evidence to show a correlation to therapeutic levels of expression of α-MHC transgene expression in an *in vivo* setting in a subject suffering from myocardial failure; further, Applicant fails to show what levels of an α-MHC transgene expression are required to alleviate myocardial failure, or a protocol for reaching such levels. The provided Declaration shows a correlation between α-MHC levels and myocardial failure; however, the Declaration fails to provide expression levels of an α-MHC transgene to reverse such failure.

Applicants argue that the Examiner has only presented a number of general gene therapy references to show the unpredictable state of the gene therapy art.

Applicant directs the Examiner to various references (see p. 5 of Applicants' response), however, as these references are not provided, the Examiner cannot offer an evaluation of them. Furthermore, it is noted that on pp. 8-9 of the prior Office action, the Examiner has supplied references with particular regard to cardiovascular gene therapy. The issues raised by these references point to the unpredictable factors in cardiovascular gene therapy, such factors include the development of gene delivery, long-term, highly-efficient and targeted expression to relevant cells, and vectors that are safe for human administration (see Nabel). Furthermore, the Examiner has provided the Applicant with post-filing art (see Hajjar) that explicitly discusses the above stated unpredictable factors regarding cardiovascular gene therapy.

Thus it is maintained that the specification fails to enable the claimed invention for the reasons of record in the prior Office action (Paper No. 5) as discussed in the preceding paragraphs.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record advanced on p. 10 of the prior Office action (Paper No. 5).

Claim 23 is incomplete. It is further unclear how the step of the method, "administering an effective amount of a transgene encoding α-MHC," correlates to the

intended effect of the method (the preamble), "treating myocardial failure" since, in light of specification, mere administration of an α-MHC transgene would not be sufficient to achieve treatment of myocardial failure without the expression of the recombinant DNA. Furthermore, the claim does not specify to what tissues the transgene would be administered.

Conclusion

Claim 23 appears to be free of the prior art of record for the reasons advanced on p. 10 of the prior Office action (Paper No. 5).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

TNT

Thaian N. Ton
Patent Examiner
Group 1632

Deborah Crouch

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